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September 30, 1999

3M

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr.
Rm. l-23
Rockville, Maryland 20857

Re: **Docket Number 99D-1738**

Subject: **3M Pharmaceuticals' Comments to Draft *Guidance for Industry – Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action***

Dear Sir/Madam,

Enclosed please find 3M Pharmaceuticals' comments on FDA's Draft *Guidance for Industry – Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.* These comments were prepared by Les Harrison, Section Head, Clinical Pharmacokinetics and Pharmacodynamics, 3M Pharmaceuticals, and are provided in reference to Docket Number 99D-1738.

3M Pharmaceuticals is a member of IPAC and has participated in the development of IPAC's comments to this draft guidance. 3M incorporates by reference IPAC's comments in this submission to the docket. It is recognized that the official comment period for this draft guidance closed on September 22, 1999, however, in concert with IPAC and in informal conversation with Dr. Wallace Adams, 3M submits these comments with the understanding that they will still be considered as Dr. Adams takes future action to define the final guidance.

Should you have any questions regarding the comments, please don't hesitate to call me.

Respectfully,

David M. Markoe, Jr.
Regulatory Specialist

cc: Wallace P. Adams
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99D-1738

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COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR NASAL AEROSOLS AND NASAL SPRAYS FOR LOCAL ACTION

Submitted By 3M Pharmaceuticals

I. BACKGROUND ON 3M PHARMACEUTICALS

3M Pharmaceutical's considerable experience with the development of the metered-dose inhaler (MDI) provides a strong knowledge base upon which to participate in the development of standards for approval of medicinal products for oral and nasal inhalation. 3M Pharmaceuticals (a.k.a. Riker Laboratories Inc.) invented the MDI in 1956 and has been engineering product innovations ever since. In the 1980s 3M Pharmaceuticals pioneered the breath-actuated aerosol MDI technology with the Autohaler™ drug delivery system. 3M Pharmaceuticals also formulated the world's first CFC-free MDI containing the drug albuterol sulfate (Airomir™ aerosol) in an HFA propellant system. This product is now approved in over 40 countries. In addition to its technological expertise, 3M have been studying aerosol performance, both in vitro and in vivo, for over 30 years.

3M Pharmaceuticals manufactures and/or sells state-of-the-art aerosol components (valves, seals, o-rings, container and closure systems, actuators, etc.) for use in its own branded products as well as in the products of its customers. 3M Pharmaceuticals estimates that it supplies components, technology, or finished aerosols in approximately 322 million MDIs sold each year throughout the world. 3M Pharmaceuticals is currently making its HFA formulation technology available to many pharmaceutical companies for use with many different drug products.

II. THE APPROPRIATE USE OF IN *VITRO* METHODS

Current *in vitro* methodology for nasal products intended for local delivery has been developed for laboratory product development and for quality control, and for these purposes, these tests work well. There are many variables that go into making a finished product (see Exhibit A) and each company develops an *in vitro* test history of their product throughout all the development stages. If these variables do not change in production, then adequate assurance of product quality can be obtained from these *in vitro* tests because of the established *in vitro* test history. Also, if small changes are made in manufacturing process or manufacturing site of the same finished product, such that only a few variables are changed, then the established *in vitro* test history of the product is still adequate to assure maintenance of product quality after the changes.

However, with a new product made by a different company, with different equipment and different sources of materials, almost all of the variables that go into making the finished product will be changed. In this case, there is no established *in vitro* test history and no means to assure maintenance of product quality with the new product based solely upon *in vitro* test results. For the purpose of bioequivalence, therefore, *in vitro* testing alone is not adequate to assure product quality BE unless a link can be established between the *in vitro* test results and the clinical relevance of the findings. The FDA has established a procedure to establish such an *in vitro-in* vivo correlation (1), and this approach must be followed prior to relying upon only *in vitro* methods to establish product quality BA and BE.

As a caution, one should in general be careful about relying upon *in vitro* data only as the sole basis for a bioequivalence assessment because of the lack of objectivity of in *vitro* tests. With an in *vivo* BE crossover study, the new and reference treatments are both randomly given to the same subjects, to provide an unbiased control. *In vitro* comparative studies have no common control and thus lack objectivity. Although multiple batches of each product are compared, there is nothing to prevent a sponsor from testing a large number of batches and arbitrarily selecting the three most advantageous batches of each product. It must be recognized that currently there is no way to prevent this bias in the assessment, which argues against relying solely upon *in vitro* measures to assess bioequivalence. It seems reasonable that the Agency consider imposing a requirement that the sponsor company submit data on all batches examined.

The appropriate use of the proposed *in vitro* testing program for nasal products is to establish only the pharmaceutical product equivalence of the test product and reference listed drug. For any nasal product, pharmaceutical product equivalence testing should encompass all aspects of characterization of the dose form: these tests include particle and droplet size distributions, spray pattern, emitted dose uniformity through the container life, priming and/or repriming characteristics relative to information in the labeling for the reference product, as well as, the emitted dose, qualitative (Q1) and quantitative (Q2) composition, and container and closure system.

Emphasis is needed on the complete dosing system equivalence because, for the unique case of nasal products, the container and closure system is an intimate part of the dose form and influences how much drug will be delivered and where drug will be delivered. The Draft Guidance should therefore specifically require equivalence of all critical dimensions of the container and closure system of the test and reference products.

III. TOO MUCH RELIANCE IS PLACED UPON *IN VITRO* PSD METHODS IN THE DRAFT GUIDANCE

The Draft Guidance assumes that *in vitro* Particle Size Distribution (PSD) methods can measure product quality BA and BE and are more sensitive and discriminating than *in vivo* methods. Compared *to in vitro* methods, clinical endpoints may be more variable and

relatively insensitive in detecting differences between products; however, this observation alone is insufficient to justify reliance upon even more problematic *in vitro* methods,

All available PSD test methods for nasal products have significant shortcomings as BA and BE metrics. The "throats" or inlet of the preferred Multistage Cascade Impaction (CI) and the Multistage Liquid Impinger (MSLI) *in vitro* PSD tests have been developed for oral inhalation products and bear no relationship to the anatomy of the nose. The test inlet flow velocity has also been developed for oral inhalation products; however, this velocity is different for products given to the nose. These observations undercut the relevance of the recommended PSD tests because it is well established that PSD can be influenced by both the shape and length of the inlet, and by flow velocity, none of which have been shown to be adequately standardized for the purposes of BE assessment of nasal products.

Another concern with the Cl and MSLI in vitro PSD tests is that the greatest percentage of the emitted dose is deposited prior to or on the first stage of the test apparatus for both nasal aerosols and sprays. This is because the stages selected for the PSD analysis are appropriate for oral inhalation, but these particle-sizing stages have not been optimized for nasal delivery. Current data indicates that larger sized particles, greater than 10 microns, are preferable for nasal bioactivity. As acknowledged on page 13 of the Draft Guidance, this is precisely the size range where the available CI and MSLI *in vitro* tests are the least precise and the least useful, as these tests do not size particles greater than 10 microns. Except that the desired size range appears to be greater than 10 microns and could be drug dependent, there is not enough scientific data to determine what is the appropriate size range for nasal deposition, There is, however, probably an upper particle size limit above which particles do not have efficacy and conceivably could be irritating.

Thus, it is ill-advised to consider the current *in vitro* CI and MSLI tests as the most sensitive tests in the BE assessment. On the contrary, one must be cautious that *the in vitro* PSD results could be insensitive and possibly misleading. For example, with the current CI and MSLI test methods given in the USP, a test product with a Mass Median Aerodynamic Diameter (MMAD) of 15 microns could not be differentiated from a reference product with a MMAD of 30 microns. Furthermore, because the *in vitro* PSD test for nasal products are not standardized, one could get different results with different methods and the results could differ depending on the product.

Given the above deficiencies in the adoption of oral inhalation PSD tests to nasal products and the lack of appropriately standardized PSD tests for nasal products, there is no scientific basis to conclude that the current *in vitro* tests are *a priori* more sensitive BE measures than clinical trials or that these in *vitro* tests are adequate to produce quality BA and BE results for nasal solution products.

IV. THE APPROPRIATE PRODUCT QUALITY BA AND BE TESTING PROGRAM

The considerable thought that has gone into the proposed *in vitro* methods in the Draft

Guidance should be more appropriately utilized to support and complement an *in vivo* BA and testing program.

At least for nasal suspension products, the Draft Guidance calls for clinical studies to compare both local delivery and systemic exposure aspects of the new and reference products. The result is a scientifically justifiable and appropriate product quality BA and BE testing program.

We recognize that the FDA has allowed BE assessment based solely upon *in vitro* testing for some solution products given by some (non-nasal) routes of administration. With the cited shortcomings of the current *in vitro* tests for nasal products, it would be inappropriate to allow BE approval for even nasal solution products based solely upon *in vitro* BE criteria. It is more reasonable to have the same guidance apply equally to both nasal solution and suspension formulations.

We strongly recommend one common BABE testing program, consisting of three BE assessments, be required for product quality BA and BE testing of all nasal products, not just suspension products. The three BE assessments are: 1) the *in vitro* methods included in the Draft Guidance, 2) a local delivery clinical study, and 3) a systemic exposure clinical study. Approval criteria would require that statistical BE tests be met for all three assessments (*in vitro*, local delivery, and systemic exposure). This common program would resolve the inconsistencies in the Draft Guidance and provide fair and objective approval criteria for all nasal products.

V. APPROPRIATE DESIGN OF LOCAL DELIVERY STUDY

The Draft Guidance attempts to describe appropriate designs for local delivery studies. To facilitate BE assessments of local delivery, more and clearer guidance is needed. An appropriate BE study with a clinical endpoint to establish equivalent local delivery of drug from test and reference products to the nose should include documentation of the sensitivity of the study design to discriminate between differing doses, This documentation typically relies upon the inclusion of a second dose of the reference product and may also include a second dose of the test product. It is appropriate to allow doses to differ by as much as fourfold and to utilize doses outside the recommended therapeutic range to increase study sensitivity.

To properly differentiate product-related findings from those occurring by chance, it is critical that a placebo treatment be included in any local delivery BE study. Such a trial, containing test and reference products and placebo, has recently been published for a test nasal formulation of beclomethasone dipropionate (2). This study design had the sensitivity to conclude local delivery BE for the test and reference nasal products,

VI. APPROPRIATE DESIGN OF SYSTEMIC EXPOSURE STUDY

The Draft Guidance recognizes that systemic exposure BE assessments can be performed for nasal products. Using current bioanalytical procedures, it is now possible to perform BE pharmacokinetic studies on nasal corticosteroid products, including budesonide (3), flunisolide (4), and triamcinolone acetonide (5); considering current assay sensitivity, beclomethasone dipropionate could probably be added to this list (6). By allowing the sponsor to study doses above the recommended therapeutic range to increase assay sensitivity, many more drugs would be able to be compared pharmacokinetically.

Certain nasal drugs have active metabolites that remain in the plasma much longer than parent drug and are more readily measured. In these instances, active metabolite as well as parent drug should be measured. A case in point is beclomethasone dipropionate (half-life of 6.6 min) and its active metabolite beclomethasone 17-monopropionate (half-life of about 2 hr) (7). The FDA has historically required active metabolites to be measured as part of BE assessments if the active metabolite contributes significantly to the activity of the product. Examples where metabolite(s) measurement as well as that of parent drug are currently required include selegine hydrochloride tablets and buspirone hydrochloride tablets.

For drugs where plasma levels are too low to permit a pharmacokinetic assessment, a systemic pharmacodynamic assessment is appropriate. For topical corticosteroids such as fluticasone propionate, for example, hypothalamic-pituitary-adrenal-axis suppression appears to be a sensitive pharmacodynamic measure that would allow systemic exposure BE product comparisons (8).

An appropriate BE study with a pharmacokinetic or pharmacodynamic endpoint to establish equivalent systemic exposure of drug from test and reference products to the nose should include documentation of the sensitivity of the study design to discriminate between differing doses. This documentation typically relies upon the inclusion of a second dose of the reference product and may also include a second dose of the test product.

VII. THE DRAFT GUIDANCE IS INCOMPLETE

The statistical requirements including the proposed upper limits for concluding BE for the *in vitro,* local delivery and systemic exposure assessments are not included in the Draft Guidance. As these statistical requirements relate directly to study designs and numbers of subjects, they must be included in any document before a complete scientific review can be performed. Since the purpose of the Draft Guidance is to solicit public review and comment and since this purpose cannot be fulfilled until the Draft Guidance is complete, the guidance must be reissued as draft with complete statistical procedures and definitions included.

Although certain aspects of the formulation (Q1 and Q2) and the container and closure system are mentioned in the Draft Guidance, the specific guidance for the CMC testing of the inevitable product changes (e.g., sources of components, elastomers, impurities and extractables) as they relate to the safety of the test product have been ignored. Section A on page 5 of the Draft Guidance, which pertains to formulation, appears to apply exclusively to suspension formulations. A comment on solution formulations is therefore needed. In addition, Section B on page 5 of the Draft Guidance, which pertains to container and closure system, does not discuss the documentation needed if elastomers and/or extractables are different from the reference product.

The Draft Guidance does not consider the required BE testing for nasal products administered to children. As it is well established that children metabolize and react to many drugs differently than adults, it is not appropriate to assume that BE results generated in adults apply equally well to children. For nasal products in particular, care must be exercised when extrapolating to the pediatric population because children breath at a different rate, have a different airflow, and potentially different nasal drug deposition because of the smaller size of the airway passages compared with adults. A proposed BE testing program in children, including at least one systemic exposure study for safety, is needed.

VIII, ADDITIONAL CHANGES AND MODIFICATIONS NEEDED

Section A on page 8 of the Draft Guidance, which pertains to batches and drug product sample collection, contains batch requirements that are inappropriate for a product quality BE assessment. For most pharmaceutical products, including nasal and oral inhalation products, the performance of commercial batches cannot always be predicted from stability and/or clinical trial batches. Because of the critical nature of this testing in the BE assessment, and because of the limited number of batches which practically can be examined, it is appropriate and fair to require production-scale batches of the test product, as well as the reference product. If the stability tests or the clinical studies on the test product were done with smaller-sized batches, then these should be tested and included in the comparison with the production batches as well.

The Draft Guidelines arbitrarily requires the comparison of three batches of test and reference product. However, 3M Pharmaceuticals manufacturing experience with the Andersen CI test shows that the between batch coefficient of variation for individual plates (with greater than 10% of the total mass) for a given product ranges from 9% to 22%. A 9% variation would require the testing of 4 batches to provide the needed sensitivity to compare two products; a 22% variation would require 15 batches. Rather than an arbitrary selection of a specific number of batches for the PSD test, a statistical justification, based on the coefficient of variation of the product, should be required for the number of batches studied.

In addition, given the history of industry/Agency collaboration with respect to the development of the SUPAC guidances and the upcoming introduction of revisions to 21 CFR 3 14.70, we suggest that the Postapproval Change section is beyond the scope of this Draft Guidance. We recommend that a stronger linkage be created between the development tests described in the Draft Guidance and the in vitro tests described in the companion Chemistry, Manufacturing and Controls (CMC) Draft Guidances For Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products, and Metered-Dose Inhaler (MDI) and Drug Powder Inhaler (DPI) Drug Products.

Finally, the Draft Guidance proposes on page 18 that fulfilling the BE requirements for local delivery for seasonal allergic rhinitis (SAR) is sufficient to grant the sponsor of the test product all the indications in the reference product labeling. This proposal does not seem to be scientifically justifiable in light of the uncertainties of the particle size distributions between test and reference products. It is conceivable that a test product could have a different PSD than the reference product that was not detected in vitro; this test product might pass a SAR clinical test, yet would fail the second indication test if this were studied. For example, Vancenase® (Schering) is indicated for the relief of the symptoms of seasonal or perennial rhinitis, but also for the prevention of recurrence of nasal polyps following surgical removal. As there is no established relationship between SAR and nasal polyps, it would not be appropriate to grant an additional indication in this case when only SAR was examined.

IX. CONCLUSION

We strongly support the Agency's efforts to develop guidance on product quality BA and BE studies for nasal aerosols and nasal sprays and appreciate the Agency's openness to accept public comments on the current Draft Guidance.

Our recommendation is for a fair and unbiased product quality BA and BE assessment for all nasal products. This would be accomplished with a BE testing program consisting of three BE assessments: 1) the *in vitro* methods included in the Draft Guidance, 2) a local delivery clinical study, and 3) a systemic exposure clinical study.

In taking the next step forward to incorporate public comments into the guidance, we strongly recommend that the Agency utilize an appropriate technical process to assemble the best available medical, pharmaceutical and academic expertise, from within and outside the FDA, to make recommendations for a revised draft.

We hope our comments will be of value to the Agency and we look forward to the ultimate publication of a final Guidance that will effectively serve the current and future needs of the inhalation drug product industry.

X. REFERENCES

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7. Agertoft A, Pedersen S, Harrison LI (1999) Lung deposition and basic pharmacokinetic parameters of beclomethasone dipropionate in asthmatic children after inhalation from a HFA p-MDI (Autohaler) and a CFC p-MDI with spacer. Am J Respir Crit Care Med 159: A120.
8. Wilson AM, McFarlane LC, Lipworth BJ (1998) Effects of repeated once daily dosing of three intranasal corticosteroids on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity. J Allergy Clin Immunol 101: 470-474.

Exhibit A

Variables to Control in Inhalation Product Manufacture

- Drug Substance
  - Synthetic Process
  - Impurity Profile
  - Specifications
  - Manufacturer
  - Manufacturing Site
  - Analytical Methods
- Drug Product
  - Qualitative Composition
  - Quantitative Composition
  - Med Delivery
  - Spray Pattern
  - Spray Force
  - Plume Geometry
  - Particle Size Distribution
  - Manufacturing Site
  - Manufacturing Process
  - Specifications
  - Test Methods
  - Container Closure System
  - Valve Size
  - Priming Characteristics
  - Process Controls
  - Component Suppliers
  - Constituent Suppliers
  - Impurity Profile
  - Degradation Products

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